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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,786	07/20/2007	Heike Gielen-Haertwig	BHC 041037	1365

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EXAMINER	
JAISLE, CECILIA M	
ART UNIT	PAPER NUMBER
1624	
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06/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,786	GIELEN-HAERTWIG ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 12-20* is/are rejected.

7)☒ Claim(s) *6-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08-25-2006 and 04-08-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Abstract

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. As an aid to future researchers, a structural formula of the claimed compounds should be given

Complete revision of the abstract content is required on a separate sheet.

Lack of Unity

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-20, drawn to compounds of Formulas (I) and (IA) in which A is phenyl, process for the preparation thereof, classified in class 544, subclasses 330, 331 and 332, pharmaceutical compositions and methods of treatment therewith, classified in class 514, subclass 269.

II. Claims 1-20, drawn to compounds of Formulas (I) and (IA) in which A is pyridyl, process for the preparation thereof, classified in class 544, subclasses 330, 331 and 332, pharmaceutical compositions and methods of treatment therewith, classified in class 514, subclass 269.

III. Claims 1-3, 6-11 and 13-20, drawn to all other Formula (I) compounds, process for the preparation thereof, classified in class 544, subclasses 330, 331 and 332, inter alia, pharmaceutical compositions and methods of treatment therewith, classified in class 514, subclass 269, inter alia.

Each group as set forth above lacks unity with each other group, i.e., there is no single general inventive concept. The unique special technical features in each group are the identities of the compounds in regard to the A ring. The technical relationship between the inventions does not involve at least one common or corresponding special technical feature. The expression "special technical feature" is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. In this case, a reference that could be used to reject the compounds, processes medicaments and uses of Group I could not be used to reject the compositions, processes medicaments and uses of Groups II-III.

The Group I invention has special technical features not common to Groups II-III and would be expected to be useful other than as disclosed, e.g., intermediates to calcium channel function inhibitors (US 20080103164).

Restriction for examination purposes as indicated is proper because the inventions listed in this action are lacking in unity and are independent or distinct

for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;
(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
(d) the prior art applicable to one invention would not likely be applicable to another invention;
(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

During a telephone conversation with Mr. William Gray on Apr. 3, 2008 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-20, drawn to compounds of Formulas (I) and (IA) in which A is phenyl, process for the preparation thereof, pharmaceutical compositions thereof and methods of treatment therewith. Applicant must affirm this election in replying to this Office action. Claims 1-20 are under examination only to the extent that they are drawn to compounds of Formulas (I) and (IA) in which A is phenyl, process for the preparation thereof, pharmaceutical compositions thereof and methods of treatment therewith. Otherwise, claims 1-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected subject matter.

Applicant is advised that a complete reply to this requirement must include (i) election of an invention to be examined though the requirement is

traversed (37 CFR 1.143) **and (ii) identification of claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the lack of unity requirement, election shall be treated as an election without traverse. Traversal must be presented at the time of election to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

If applicants traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions are obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.
Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objectionable Claims

Claims 6-11 are objected to under 37 CFR 1.75(c) as being in improper form, because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 6-11 have not been further treated on the merits.

Rejections Under 35 USC 101

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17-19 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth steps involved in the process, results in an improper process definition, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* and *in vivo* inhibition of neutrophil elastase in murine models, does not reasonably provide enablement for a

process for controlling obstructive pulmonary disease, acute coronary syndrome, acute myocardial infarction or development of heart failure in humans and non-murine animals by administration of a neutrophil elastase [NE] inhibitory amount of a compound of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following reasons apply to this enablement rejection.

Many diseases said to be controlled by the claimed compounds, such as COPD, are known as difficult to treat. At present no known drug can successfully prevent or reverse the course of many of these diseases. See Eur. Resp. Soc., http://www.newtocopd.com/currentaffairsnews/list751_item17680.aspx, downloaded 1/15/08, "… there are currently no effective treatments for COPD …"

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. This disclosure is not sufficient to enable the claimed methods based solely on the disclosed activity.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration to determine whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) claim breadth; (2) nature of the invention; (3) state of the prior art; (4) level of predictability in the art; (5) amount of direction provided by the inventor; (6) presence of working examples; and (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (CAFC 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement.

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover pharmaceutical methods using thousands compounds of Formulas (I) and (IA) in which A is phenyl.

(b) Scope of the diseases covered. The diseases construed by the claims have been described above. The specification fails to identify results

of treatment with the methods of this invention in humans and non-murine animals.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is considered an unpredictable factor. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** The art indicates the need for undue experimentation.

Regarding NE inhibition and obstructive pulmonary disease, Roghanian, et al., Am. J. of Respiratory and Critical Care Medicine, Vol. 174, 2006, 1189-1109, describe an area for clinical future research:

> In conclusion, our data show that NE and NE-containing secretions from patients with COPD [chronic obstructive pulmonary disease] or CF [cystic fibrosis] can disable DC [dendritic cell] function by interfering both with the ability of immature DCs to mature in

> response to bacterial LPS stimulation, and by reducing the antigen-presenting activity of mDCs. Although the in vivo effects of these changes remain to be investigated, the reduced Th1 cytokine levels includes by NE treatment of CDs may, in part, explain the reported Th2 imbalance in the lung immune response to bacteria inpatients with CF and the reported loss of IFN-λ-secreting cells in patients with COPD. This local Th2-biased phenotype may be instrumental in the inability of these patients to clear semifacultative intracellular pathogens in the lung … as suggested recently by a variety of animal and human studies. In that context, our strategy of overexpression of the elastase inhibitor, elafin, could be dually advantageous by inhibiting NE and, as shows recently, by providing a Th1-biasing signal in the lungs.

Regarding NE inhibition and acute coronary syndrome, Hsieh, et al., Bioorganic & Med. Chem. Lett., 17 (2007) 1812-1817, state, "Arterial thromboembotic diseases, for example, acute coronary syndrome and ischemic stroke, which are caused by platelet aggregation, are the major causes of death in developed countries." Hsieh tested the 2-benzoylamino-benzoid acid derivates, 6d and 6e (Table 2), and reported, "[C]ompounds 6d and 6e exhibited dual inhibitory effects on platelet aggregation and NE release; therefore, these two compounds may represent new leads for development as anti-inflammatory and anti-platelet aggregatory agents."

Regarding NE inhibition and acute myocardial infarction, Vermeylen, et al., J. of Thrombosis and Haemostasis, 3: 1955-1961, 2005, reported, "Specific neutrophil elastase inhibition in the lung did not affect lung inflammation, but reduced peripheral thrombogenicity, suggesting that in this instance neutrophil elastase could have a role as platelet 'primer', as suggested by previous *in vitro* investigations."

Regarding NE inhibition and heart failure, Kyne, et al., Am. Heart J., 139(1):94-100, 2000, reported:

> The results suggest that relative neutrophilia may serve as a simple, noninvasive marker to identify patients who are at high risk for development of CHF [congestive heart failure] after myocardial infarction. If the peripheral neutrophil count truly reflects the myocardial inflammatory response, future interventions that are designed to limit this response could help to reduce morbidity and mortality rates associated with CHF occurring after AMI [acute myocardial infarction].

The ability of an agent that exhibits activities shown in the specification to treat all diseases-conditions construed by the claim, especially in humans and non-murine animals, remains open to further study and proof.

5. **Working Examples:** Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.

6. **Skill of those in the art:** Roghanian, Hsieh, Vermeylen, the American Heart Journal and the European Respiratory Society question the ability of a single class of compounds to effectively treat all types of diseases and/or conditions construed by the claim; they confirm the need for additional research.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed herein, indicates the requirement for undue experimentation.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

Claims 1-5 and 13-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Formula I and IA compounds and their salts and tautomeric forms, does not reasonably provide enablement for hydrates and solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace hydrates and solvates, are not enabled. The specification prophesizes hydrates and solvates, but the examples presented all failed to produce a hydrate or solvate. The evidence of the specification is clear: These compounds do not possess the property of forming hydrates and solvates; no evidence shows that hydrates and solvates even exist.

This is a circumstance where the "specification is evidence of its own inadequacy" (*In re Rainer*, 153 USPQ 802, 807). Hydrates and solvates cannot be simply willed into existence. *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 states:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist ... the examples of the '881 patent do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The same circumstance appears true here: no evidence shows that hydrates and solvates of these compounds actually exist; if they did, they would have formed. Applicants must show making hydrates and solvates or limit the claims accordingly.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-19 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim subject matter which applicant regards as the invention. Claims 17-19 attempt to claim a process without setting forth steps involved in the process, which raises an issue of indefiniteness. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986).

Rejections Under 35 USC 102

The following is a quotation of the appropriate paragraph of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5 and 12-20 are rejected under 35 USC 102(e) over Gielen-Haertwig, WO2004024700, entitled to the 08-28-03 filing date. Gielen-Haertwig

describes pyrimidinone compounds of Formula I in which each of the substituents encompass the substituents of the presently claimed compounds.

Obvious Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 and 12-20 are rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 1-21 of US 10/527391. The conflicting claims overlap each other and are not patentably distinct from each other. There is no patentable distinction between the US 10/527391 compound claims 1-21 and the present application Claims 1-5 and 12-20. Because neither application is patented, this rejection is provisional.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

5/2/2008

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624